Disease Name — Methylmalonic acidemia, Vitamin B-12 non-responsive

Alternate name(s)	Methylmalonic aciduria due to methylmalonic CoA mutase deficiency, Complementation group mut0, Methylmalonyl-CoA mutase
Acronym	MMA
Disease Classification	Organic Acid Disorder
Variants	Yes
Variant name	Vitamin B12 metabolic defect with methylmalonic acidemia and homocystinuria
Symptom onset	Eighty percent of infants become ill during the first week or life and 90% will present by the end of the first month. Infants with the less severe *mut*- may present later than the first month. A few may remain asymptomatic or present much later in life depending on the residual enzyme activity and the metabolic stressors.
Symptoms	Most common signs and symptoms are lethargy, failure to thrive, recurrent vomiting, dehydration which leads to profound metabolic acidosis, respiratory distress, hypotonia and death if not recognized. Complications of acute episodes can include metabolic stroke, extrapyramidal signs, dystonia and bilateral lucencies of globus pallidus. Survivors may have significant neurological damage. Renal failure may appear during childhood. Clinical spectrum is wide, ranging from fatal neonatal disease to asymptomatic individuals. Patients do not have to have clinical crises in order to have neurological or other organ compromise.
Natural history without treatment	Variable depending on the enzyme defect and the patient. Some will die as a neonate, others will survive with deficits and a few others will remain asymptomatic.
Natural history with treatment	About 60% of patients die within the first year of life and of those that survive, 40% are distinctly developmentally impaired. Age of onset of symptoms can help prognosticate – those with later onset tend to have a more benign course. Liver and liver/kidney transplant are one treatment option. However, liver transplants have significant preoperative risk and there is documentation of neurological problems after transplant despite improved biochemical values. Renal transplants have shown good response with drops in methylmalonic acid levels, normalization of the diet and absence of acute episodes of metabolic decompensation. However, the effect of any type of transplant is limited because the MMA enzyme is in all tissues and the transplants do not affect the levels made in the cerebro-spinal fluid and brain.
Treatment	Protein restricted diet, OH-Cbl injections, carnitine supplementation and oral antibiotic therapy to decrease gut production of propionate. Special medical foods (formula) deficient in methionine, threonine, valine, isoleucine, odd chain fatty acids and cholesterol. Liver transplant and liver/kidney transplant.
Other	N/A
Physical phenotype	Most patients have no obvious dysmorphic features. Some patients, in whom there is known consanguinity, have had associated birth defects, congenital heart defects, hydronephrosis and facial dysmorphisms.
Inheritance	Autosomal recessive
General population incidence	1:48,000
Ethnic differences	None known
Population	N/A
Ethnic incidence	N/A
Enzyme location	Liver, kidneys, cerebrospinal fluid, brain
Enzyme Function	Catalyzes methylmalonyl-CoA to succinyl-CoA
Missing Enzyme	Methylmalonyl-CoA mutase
Metabolite changes	Increased methylmalonic acid in blood and urine.
Gene	MCM
Gene location	6p12-q21.2
DNA testing available	Sequencing available internationally
DNA testing detail	N/A
Prenatal testing	Possible via enzyme assay on amniocytes or CVS..
MS/MS Profile	Elevated C3 propionyl carnitine, elevated C4 DC methylmalonyl carnitine.
OMIM Link	www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=251000
Genetests Link	www.genetests.org
Support Group	Organic Acidemia Association www.oaanews.org Save Babies through Screening Foundation www.savebabies.org Genetic Alliance www.geneticalliance.org